ENCEPHALITIS AND CEREBELLAR ATAXIA ASSOCIATED WITH EPSTEIN-BARR VIRUS INFECTIONS

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ENCEPHALITIS and cerebellar ataxia are rare complications of infectious mononucleosis (IM). Until recently the demonstration of a raised titre of heterophil antibodies in a Paul-Bunnell test provided the best objective data for substantiating a diagnosis of IM. Unfortunately, this test may produce both false positive and false negative results and may remain positive for many months after the acute phase of the illness. Epstein-Barr virus (EBV) is a member of the herpes group of viruses and is the causal agent of IM. The development of specific serological tests has allowed a more precise determination of the temporal relationship between EBV infection and various complications. We report two teenage boys who had encephalitis and cerebellar ataxia associated with EBV infections.

METHODS AND CASE REPORTS

The method was based on that of Schmitz and Scherer (1972) with modifications. P3HR-1 lymphoblastoid cells were grown in suspension culture at 33°C for three days to express Epstein-Barr virus antigen. Cells were air dried on coverslips and fixed in acetone for 10 minutes. Sera and CSFs were absorbed with human brain powder, and for detection of EBV immunoglobulin M (IgM) they were further absorbed with heat aggregated human immunoglobulin to remove rheumatoid factor, and with Protein A-Sepharose (Pharmacia) to reduce the immunoglobulin G (IgG). Sera and CSF dilutions were allowed to react with P3HR-1 coverslips for one hour at 37°C for detection of EBV specific IgG and for three hours at 37°C for detection of EBV specific IgM. After washing, fluorescin conjugated sheep anti-human IgG or IgM was allowed to react with the P3HR-1 coverslips for one hour at 37°C, then washed off. Coverslips were mounted in glycerol-saline and viewed with an epifluorescence microscope.

Poliovirus type 2 neutralising antibody was titrated as described by Connolly, Robinson and Canavan (1975). All antibody titres are expressed as reciprocals of 50 per cent endpoint dilutions.

PATIENT 1

A previously fit 15 year old schoolboy was admitted to Craigavon Area Hospital in a semi-conscious state on 8th February 1979. Twenty-four hours previously he developed an upper respiratory tract infection. Twelve hours before admission he

developed headache and vomited on three occasions. He then became progressively more drowsy and about two hours before admission he developed bizarre movements of the limbs and was incontinent of urine.

On admission he was restless, semi-conscious, responding only to painful stimuli. His temperature was 40°C. There was no neck stiffness. Optic fundi were normal. Pupils reacted normally to light. His reflexes were brisk and symmetrical and plantar responses were flexor. He had a few palpable glands in the left axillae but there was no rash and no splenomegaly.

The full blood picture was haemoglobin 14.7 g/dl., WCC 15.1 $\times$ 10^9/l., (75% neutrophils, 15% lymphocytes, 7% monocytes and 3% mononuclears). Electrolytes, urea and blood glucose were normal. He had a lumbar puncture and the CSF was reported as follows:- Clear colourless fluid, red blood cells nil, white cells 6 lymphocytes/mm^3, protein 0.1 g/l, globulin nil, and sugar 4.4 mmol/l. The electroencephalogram (EEG) was abnormal with irregular theta activity at 4-6 c/s. and persistent high amplitude paroxysmal slow activity at 1-3 c/s. bilaterally. He was treated with dexamethasone and chlorpromazine. His level of consciousness slowly improved over the following five days but he remained disorientated in time and place. His memory was poor and he was ataxic, being unable to stand or walk unaided and had difficulty feeding himself. He had some aggressive outbursts.

Blood picture on 14th February 1979 was as follows:- Haemoglobin 15 g/dl., WCC 14.4 $\times$ 10^9/l (44% neutrophils, 24% lymphocytes, 13% monocytes, 1% eosinophils, 1% basophils and 17% mononuclears). The Paul-Bunnell test was positive. The titre in saline was 160, after absorption with guinea pig kidney—80, and after absorption with ox cells—nil. Serum complement fixing antibody titres to mumps, measles, herpes simplex and varicella-zoster virus antigens were not significant.

On the sixth day he had a sudden convulsion which progressed to status epilepticus and did not respond to intravenous diazepam. Treatment with muscle relaxants, intermittent positive pressure ventilation and ACTH was started.

Lumbar puncture was repeated on 15th February 1979 and the CSF was reported as follows:- Clear colourless fluid, red blood cells 21/mm^3, white cells—7 lymphocytes/mm^3, protein 0.35 g/l., globulin—trace, sugar—insufficient for examination. No organisms were seen.

Intermittent positive pressure ventilation was withdrawn after 48 hours but the ACTH was continued for a further five days. Anticonvulsant therapy with oral phenytoin sodium was commenced.

The patient's condition improved rapidly and on discharge 15 days after admission his gait was steady and his mental state had returned almost to normal. At review on 15th March 1979 his mental state had returned to normal and no neurological sequelae were present, although his EEG still showed a mild generalised abnormality. A follow-up EEG nine months later (13th December 1979) was normal.

PATIENT 2

A 17 year old schoolboy was admitted to Coleraine Hospital on 5th February 1979. His illness had begun six days earlier with general malaise and recurrent pain in the left lower chest, aggravated by breathing and slight temperature. For two days before admission he was vomiting frequently and was unable to eat. His chest pain had settled and he had no sore throat, but felt ill and dizzy.

On admission he was afebrile. He was mentally clear but apathetic. He was pale, sweating and slightly tremulous. There was no neck stiffness but he had a few shotty, deep cervical glands. His heart sounds were normal and he had a faint pleural rub in the left lower chest. Liver and spleen were not palpable. CNS findings were negative. On the day following admission he continued to have nausea and vomiting and had a faint macular rash on his trunk. That afternoon he suddenly had a fit which lasted for about five minutes, with right sided twitching. Thereafter he was stuporous, restless and aggressive. His temperature rose to 40°C that evening. His plantar responses became extensor.

A lumbar puncture gave clear CSF with 10 white cells/mm^3, protein 1.4 g/l., sugar 3.7 mmols/l. The blood picture was—Hb. 14.6 g/dl., WCC 12.1 $\times$ 10^9/l., (neutrophils 36%, lymphocytes 54%, monocytes 10%). More than half of the lymphocytes were abnormal virocytes. Mononuclear cells were normal. The sedimentation rate was 3 mm/hr. Chest x-ray was normal. The ECG showed changes in keeping with pericarditis. These changes were later confirmed and subsequently became normal.

Two days after admission he remained irritable and inaccessible, reacting only to painful stimuli. His optic fundi were normal and there was no neck stiffness or other localising CNS findings.

He was transferred that day to the Neurological Department of the Royal Victoria Hospital under the care of Dr. M. Swallow. He was then stuporous and irritable and the general findings were unaltered. His temperature remained elevated for two more days and he then became more responsive and alert. His speech was slow and slurred and there was ataxia of his upper limbs but no nystagmus. The abnormal white cell count improved and a Paul-Bunnell test was positive (titre 128). Serum complement fixing antibody titres to mumps, measles, herpes simplex and varicella-zoster virus antigen were not significant. Virus was not isolated from faeces or CSF. The EEG was reported as follows:- "The patient was semi-conscious. The record is dominated by delta wave complexes at ½-2 Hz of amplitude up to 200 /uv which have at times a sharp quality. The complexes are seen bilaterally, though asynchronously. There is no focus or lateralisation. The record shows a marked generalised abnormality, which is typical of that seen with an inflammatory condition".

He continued to make a gradual recovery without any specific treatment. A week after admission he was still irritable, his speech was still very slurred and he had some headache. He was discharged from hospital after six weeks, at which time his speech and gait were normal and there was no ataxia. Six weeks later he still felt 'slow' mentally and physically. Three months after discharge he felt normal.

RESULTS OF SEROLOGIC STUDIES

The EBV and poliovirus type 2 antibody titres in serum and CSF are shown in the table.

TABLE

Patient	*Day of Illness*	*Specimen*	*EBV Antibody IgG*	*EBV Antibody IgM*	*Poliovirus type 2 antibody*
1	2	Serum	<10	10	—
	12	Serum	80	40	—
	310	Serum	80	<10	—
2	9	Serum	160	40	5120
	9	CSF	4	0	16

In patient 1 there was a >8 fold rise of EBV specific IgG between day 2 and day 12 and this antibody was still present at day 310. The EBV specific IgM showed a 4-fold rise between day 2 and day 12 but had disappeared by day 310. There was EBV specific IgG in the serum and CSF of patient 2 on day 9 and the serum/CSF ratio was 40. Poliovirus type 2 antibody was also present in serum and CSF and the serum/CSF ratio was 320. There was EBV specific IgM in the serum of patient 2 but not in CSF.

DISCUSSION

The diagnosis of encephalitis in both patients was made from the clinical features and the abnormal EEGs. There was gross disturbance of consciousness in both patients but no physical signs of meningitis. Patient 2 had a right sided focal fit and patient 1 had status epilepticus. Aggressive behaviour was also present in both patients. Cerebellar ataxia was noted in arms and legs of patient 1 and in the arms of patient 2. In both patients the CSF had increased white cells and the protein was increased in patient 2. Both patients recovered completely, although in patient 1 the EEG was still abnormal 36 days after onset and patient 2 still felt 'slow' mentally and physically 66 days after onset. The prognosis of neurological complications of IM is reported to be good and death is rare.

The diagnosis of IM was suspected from the clinical features of patient 2 but not in patient 1. Both patients had raised white cell counts in blood. Patient 2 had abnormal lymphocytes in the blood films and both patients had positive Paul-Bunnell tests. The 4-fold or greater rise of EBV specific IgG and IgM in patient 1 indicates a recent infection with this virus. The presence of EBV specific IgM in the serum of patient 2 also indicates recent infection with this virus. The EBV specific IgM response is transient in acute IM and disappears in about 2-3 months after onset (Schmitz and Scherer, 1972) even in those cases without heterophil antibodies (Nikoskelainen, Leikola and Klemola, 1974). Poliovirus neutralising antibody can be used as an unrelated marker for an intact blood-brain barrier. Clarke, Dane and Dick (1965) found that there is a poliovirus serum/CSF antibody ratio ranging from 256 to 2048 in healthy people if serum and CSF samples are taken at the same time from the patient. The poliovirus type 2 serum/CSF ratio in patient 2 was 320, which excludes contamination of the CSF with blood when the sample was taken and also a non-specific leak of serum antibody into the CSF possibly due to inflammation of

the blood brain barrier. The EBV IgG serum/CSF ratio on the other hand was 40, which is eight times lower and indicates either that EBV IgG antibody was being produced or released inside the CNS or there was selective permeability through or specific transport of EBV IgG across the blood brain barrier.

It has been estimated that the nervous system is involved in about one per cent of patients with IM who are admitted to hospital with complications (Gautier-Smith 1965, Schnell et al 1966). When there is involvement of the nervous system the usual symptoms and signs of IM although present may be overshadowed by the clinical features of the neurological syndrome. The neurological involvement described in IM may be an acute psychosis with aggressive and irrational behaviour, fits or the Guillane-Barré syndrome. Meningoencephalitis, transverse myelitis, acute cerebellar syndrome or Bell's palsy have also been described (Schnell et al 1966, Grose et al 1975). Chorea (Friedland and Yahr 1977) and retrobulbar neuritis (Pickens and Sangster 1975) have also been reported.

Encephalitis was first described in association with glandular fever by Epstein and Dameshek (1931) and approximately 100 cases had been described up until 1954, although very few were in children (Walsh, Poser and Carter 1954). Custer and Smith (1948) described the pathology in fatal cases of IM. In the brain signs of acute inflammation were absent or minimal, and there was some perivascular cuffing with inflammatory cells. Sworn and Urich (1970) describe a true polio-encephalitis in a fatal case with perivascular cuffing and infiltration of the brain parenchyma with inflammatory cells, while Ambler et al (1971) describe an inflammatory demyelinating lesion in an occipital lobe biopsy which was consistent with an allergic or post-infectious encephalomyelitis. The biopsy was taken during convalescence from IM. EBV has been isolated from the CSF in encephalitis (Halstead and Chang 1979). In three patients EBV infection has been associated coincidentally with subacute sclerosing panencephalitis (SSPE). Hochberg et al (1976) describe herpes type particles in the brain of SSPE and EBV antigen in addition to measles virus.

Involvement of the cerebellum in IM is very rare and few patients with clinical evidence have had serological confirmation of EBV infection (Lascelles et al 1973, Bajada 1976, and Cleary, Henle and Pickering 1980). Dowling and Van Slyck (1966) reviewed six cases from the literature of cerebellar involvement, where the Paul-Bunnell test was used for diagnosis. In fatal case of IM, Bergin (1960) refers to oedema or degeneration of the Purkinje cell layer of the cerebellar cortex and perivascular inflammation. Patient 2 had EBV specific IgG in serum and CSF, and EBV specific IgM in serum but not in CSF. CSF-EBV antibody has also been found by Lascelles et al (1973), Joncus et al (1974) and Hochberg et al (1976) but not by Bajada (1976) or Cleary, Henle and Pickering (1980).

In one study of primary EBV infections in acute neurologic diseases of 14 patients (Grose et al 1975) it was found that only one patient had obvious clinical IM and only five patients had heterophil agglutinins. It is now clear that about 10 per cent of young adults and a substantially greater proportion of paediatric patients with the disease do not develop heterophil antibodies (Grose et al 1975, Lange et al 1976).

It is obvious that EBV infection must be considered in the diagnosis of various acute neurological diseases affecting children and young adults even in the absence of a heterophil antibody response or other signs of IM.

SUMMARY

Two teenage boys had encephalitis and cerebellar ataxia associated with EBV infections. The clinical signs and blood picture were not typical of infectious mononucleosis in one boy, although both boys had positive Paul-Bunnell tests. Recovery was complete in both boys but abnormalities of the EEG were still present 36 days after onset in one boy while the other boy felt 'slow' mentally and physically 66 days after onset. A rising titre of EBV specific IgM and IgG was found in one boy. The other boy had EBV specific IgM in his serum and EBV specific IgG in his CSF, which was there in excessive quantity in relation to his serum EBV specific IgG. This indicates that EBV specific IgG was being produced or released inside the CNS. There may also have been selective permeability or specific transport of EBV specific IgG across the blood brain barrier.

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